Attorney's Docket No.:0004.0001-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Victor L. Serebruany		
Application No.:	10/811,563	Group:	1628
Filed:	March 29, 2004	Examiner:	Pagonakis, Anna
Confirmation No.:	1385		

For: TREATING VASCULAR EVENTS WITH STATINS BY INHIBITING PAR-1 AND PAR-4

DECLARATION UNDER 37 C.F.R. §1.132 OF VICTOR L. SEREBRUANY

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Victor L. Serebruany, of West Friendship, Maryland, state and declare:

1. I am the inventor of the above-referenced patent application.

2. I received my medical degree in 1982 from the Medical Institute of Moscow, and my Ph.D. in 1989 from Institute of Pediatrics & Children's Surgery of Moscow. I was a Postdoctoral Fellow at the Division of Cardiology, at University of Maryland, and a Senior Research Assistant , Division of Pediatric Nephrology, at Johns Hopkins University. I am the recipient of a number of awards such as the Pfizer Established Investigator Award, Bristol-Myers Squibb Stipend, International Pediatric Nephrology Association Award, and Bristol-Myers Squibb Young Investigator Award. I am currently the owner of my research company, Heartdrug Research, LLC, and my company is conducting a number of research projects in the area of platelets. I have

authored more than a hundred articles, a partial list of which is attached to my Curriculum Vitae, attached hereto as Exhibit A. I am also a reviewer for several journals including JAMA, Circulation, Journal of American College of Cardiology, Stroke, American Journal of Cardiology, American Heart Journal. A more complete list of journals for which I am a reviewer is also included in Exhibit A. With my 28 years of experience, I am considered an Expert in the field of platelets.

3. I am also the author of the journal article, " Absence of Interaction Between Atorvastatin or Other Statins and Clopidogrel", *Archives of Internal Medicine,* 164:2051-2057 (2004), attached as Reference AX5 of the Supplemental Information Disclosure Statement filed herewith.

4. I have reviewed the Patent Application and the Office Action dated on November 10, 2009, for the above-referenced case. I have also reviewed the references cited in the Office Action, including, Birnbaum *et al* (Cardiovascualr Drugs and Therapy, 17, 25-30, 2003) hereinafter "Birnbaum" and Kahn *et al* (Journal of Clinical Investigation, Vol. 103, No.6, 1999) hereinafter "Kahn".

5. The Examiner rejected Claims 1, 5-10, 12, 14 and 22-23 under 35 U.S.C. §103(a) as being unpatentable over Birnbaum in view of Kahn. The Examiner states that Birnbaum teaches a method of reducing myocardial infarction size in an individual comprising administering a dose of atorvastatin and with regards to the dose, Birnbaum teaches that the dose of atorvastatin is 10-75 mg/kg/d; however, the Examiner states that Birnbaum does not teach selecting a patient with elevated PAR-1 and PAR-4 levels. Furthermore, the Examiner states that Kahn teaches that platelet dependent arterial thrombosis underlies myocardial infarctions (page 879, column 1), and that it was demonstrated that PAR-1 and PAR-4 are functionally expressed in human platelets, and that these receptors account for most if not all thrombin signaling in these cells. Page 885, column 1 of Kahn, Office Action, page 3. Thus, according to the Examiner, one of ordinary skill in

the art would have been motivated to select patients with elevated PAR-1 and PAR-4 levels because the activated PAR-1 and PAR-4 activate thrombin which activated platelets which, in turn, is the underlying cause of myocardial infarction.

4. I respectfully disagree.

5. As an expert in the field of platelets, I would not have expected this association, namely that statins reduce PAR-1 or PAR-4 levels. Birnbaum describes how myocardial infarct size deceases under certain dosages of statin and if administered within a certain time frame. Khan discloses roles of PAR-1 and PAR-4 in activation of human platelets by thrombin. However, there is no link between statins and platelet receptors in the cited art, and in particular between statins and PAR-1/PAR-4.

6. In this study set forth in Reference AX5, we set out to assess the interaction between Clopidogrel and statins. We assessed a number of platelet receptors in patient groups that were taking statins and those that were not taking statins. Referring to Table 2, there was no statistical significance in any platelet receptor except PAR1 and/or PAR-4 in patients on statins and those not receiving statins. The effect of statins on PAR1 and/or PAR-4 was surprising and unexpected. We made the observation accidently, when trying to solve a totally different problem, namely to determine the interaction between Clopidogrel and statins.

7. During my many years studying platelets, as an expert, I could not have made the connection without the data that supports the claimed invention.

8. The selection of patients having an elevated level of PAR-1 and/or PAR-4, and to assess the need for statin administration was not contemplated by me in light of Birnbaum and Kahn.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Victor L. Serebruany, MD, PhD

May 3, 2010

Date